Leukemia Research Reports 2 (2013) 4–6

Contents lists available at SciVerse ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Case report

Hemophagocytic lymphohistiocytosis masquerading as progressive chronic lymphocytic leukemia

Deepak Kilari [a,*], Nicholas Venci [b], Jonathan Friedberg [a], John M. Bennett [a,c]

[a] Division of Hematology/Oncology, University of Rochester, Wilmot Cancer Center, Rochester, NY, USA
[b] Department of Internal Medicine, University of Rochester Medical Center, Rochester, NY, USA
[c] Division of Hematopathology, University of Rochester Medical Center, Rochester, NY, USA

ARTICLE INFO

Article history:
Received 30 September 2012
Received in revised form
25 October 2012
Accepted 30 October 2012
Available online 5 January 2013

Keywords:
HLH
CLL
Fevers
Pancytopenia and hematologic malignancies

ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal syndrome characterized by a non-malignant expansion of the macrophage population in the setting of a heightened cytokine response with subsequent widespread hemophagocytosis. It can occur as either genetic or acquired forms; the latter of which frequently occurs in the setting of infection, autoimmune disease, or malignancy. We present the second known case of HLH associated Chronic Lymphocytic Leukemia (CLL) in the absence of infectious etiology and review the current literature.

1. Case report

A previously healthy 47 year-old male was diagnosed with symptomatic Rai stage 1 CLL after he presented with progressively worsening cervical adenopathy. He was treated with Fludarabine and mitoxantrone with a complete remission that lasted almost 12 years. Subsequently he had 2 relapses requiring treatment with R-CHOP (rituximab, cyclophosphamide, vincristine, adriamycin and prednisone) and bendamustine/rituximab. On both occasions transformation was ruled out and the patient achieved only a partial remission that lasted approximately 30 months each time.

He was doing fairly well until the age of 63 years when he presented with progressive B symptoms and was diagnosed with progressive CLL. In view of the previously prolonged complete remission enjoyed after purine analogue therapy he was started on pentostatin, cyclophosphamide and rituximab. After two cycles not only were his symptoms persistent but radiographic imaging showed progressive disease in addition to a new onset pancytopenia.

During a routine clinical evaluation he reported fevers and was subsequently admitted with neutropenic fever and hypoxia presumed to be secondary to *Pneumocystis carinii* pneumonia. His blood work on admission was significant for a white blood cell count of 1.2×10^9/L, absolute neutrophil count of 0.6×10^9/L, hemoglobin of 8.2 g/dL, and a platelet count of 37×10^{12}/L. He was empirically treated with broad-spectrum antibiotic, antiviral and antifungal therapy. Extensive workup for an infectious cause of fevers which included adenovirus, parvovirus B19, human herpes virus -6, HIV, histoplasma, Cryptococci, aspergillus, respiratory syncytial virus, influenza and legionella was all non-revealing. His hypoxia improved after several days; however he continued to remain febrile and pancytopenic despite multiple transfusions.

Given his unexplained cytopenias 30 days after completion of chemotherapy even with subcutaneous granulocyte colony stimulating factor and worsening clinical picture, a bone marrow biopsy was performed suspecting progressive marrow involvement with CLL versus transformation versus delayed recovery from chemotherapy. The biopsy however, did not show changes compared to previous biopsy in terms of percent CLL involvement (Fig. 1). Additional studies on the marrow noted a prominent population of CD68+ macrophages (Fig. 2) with active hemophagocytosis (Fig. 3). This finding, in combination with cytopenias led to further studies which included elevated serum ferritin (13,000 ng/ml), triglycerides (319 mg/dl), and hypofibrinogenemia (145 mg/dl) all pointing to the diagnosis of HLH.

As per the HLH-2004 guidelines (which reports the use of dexamethasone, etoposide and cyclosporine for 8 weeks, with

* Correspondence to: Division of Hematology/Oncology, Wilmot Cancer Center, 601 Elmwood Ave, P.O. Box 704, Rochester, NY 14642, USA.
Tel.: +1 585 275 3069; fax: +1 585 273 1051.
E-mail address: deepak_kilari@urmc.rochester.edu (D. Kilari).

2213-0489
http://dx.doi.org/10.1016/j.lrr.2012.10.003

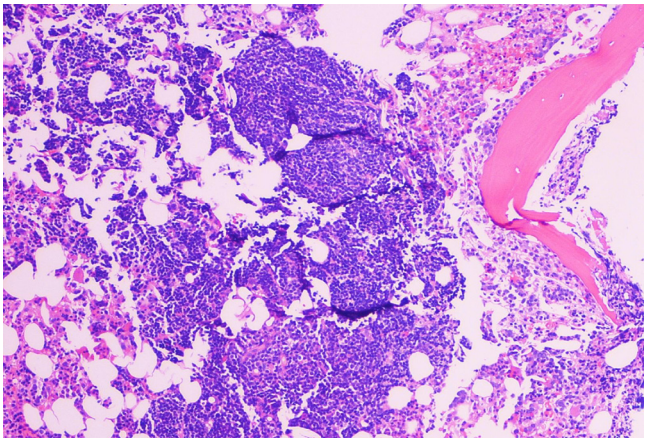

Fig. 1. Bone marrow biopsy: hematoxylin and eosin stain (400 ×): large lymphoid cluster replacing marrow with scattered mononuclear cells with abundant cytoplasm.

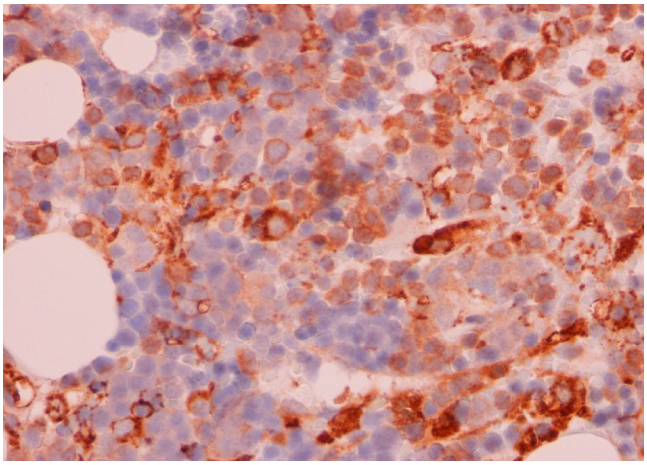

Fig. 2. Bone marrow biopsy: immunoperoxidase (400 ×): numerous histiocytes stained with CD68 antibody.

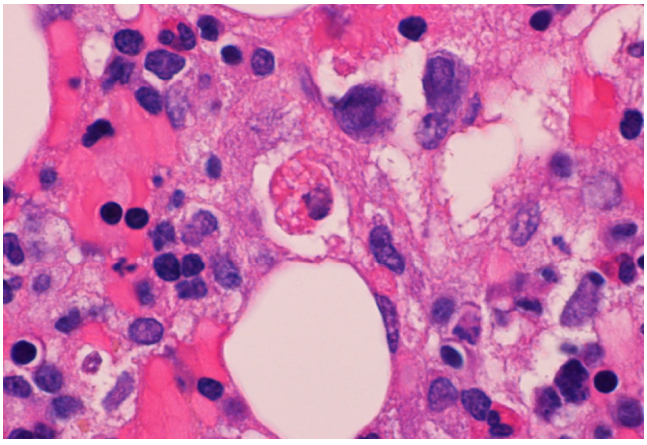

Fig. 3. Bone marrow biopsy: hematoxylin and eosin stain (1000 ×): histiocyte with numerous erythrocytes.

subsequent intrathecal methotrexate and stem cell transplant), patient was initially treated with cyclosporine and dexamethasone for several days with poor clinical and hematologic response.[1] The literature was reviewed again and it was felt that the patient's HLH could be a secondary phenomenon related to his underlying CLL and the decision was made to pursue aggressive treatment of CLL. He received one cycle of R- CHOP with continued deterioration of his clinical status over the next 3 weeks leading to acute renal failure and respiratory failure, requiring intubation. Given his poor prognosis he was transitioned to comfort care and passed away shortly thereafter.

2. Discussion

HLH in both, genetic and acquired forms can occur in the setting of infection, autoimmune disorders and occasionally hematologic malignancies. HLH is suspected to be secondary to defective NK cell removal of antigen stimulation (through perforin dependent cytotoxicity) which in turn causes persistent T cell activation, macrophage proliferation and hemophagocytosis. The organ dysfunction is attributed to high levels of cytokines, in particular soluble interleukin 2 (SIL2) which has been shown to correlate with prognosis.

HLH generally affects children; however cases of older adults with this disease have also been reported. Infectious agents typically involved include Epstein Barr Virus (EBV), cytomegalovirus, parvovirus B19 and HIV. Bacteria, parasitic, and fungal pathogens have also been implicated.[2] Extensive evaluation for underlying infection was unrevealing in our patient. In previous reports lack of infection was linked to adverse outcomes.

Malignancy associated HLH represents a heterogeneous group of mostly hematologic malignancies with the hemophagocytic syndrome appearing either before or during treatment. The clinical course in most of these patients is complicated by infections which can shadow the diagnosis of HLH. T-cell lymphoma associated HLH both with and without EBV positivity has been well documented.[3,4] In comparison, only a few cases of B-cell lymphoma associated HLH have been reported and are predominantly of the large B cell histologic subtype.[5] HLH in association with acute myeloid leukemia is rare and little is known of outcomes.[6]

The International Histiocyte society mandates five of the following eight criteria to make a diagnosis of HLH: fevers, cytopenias of at least two cell lines, evidence of hemophagocytosis, hypertriglyceridemia and/or hypofibrinogenemia, hyperferretinemia, elevated SIL2, decreased NK cell activity and splenomegaly. Our patient had six of the eight criteria, and SIL2 levels were not checked.

CLL associated HLH was first documented in the form of a case series report which included six patients treated for CLL who subsequently developed the phagocytic syndrome months to years later.[7] As these cases occurred prior to publication of the 1991 HLH diagnostic guidelines, the authors postulated that the syndrome was likely reactive to an occult opportunistic viral infection and only subsequently suspected HLH. Subsequent case reports describe CLL associated HLH only in the setting of infection.[8,9]

The present report describes "HLH associated CLL" in the absence of an ongoing infectious process. Such an occurrence has only been reported once by Meki et al. [10] In both situations the patients were initially treated per HLH-2004 guidelines.

3. Conclusion

HLH continues to present diagnostic and therapeutic challenges. To our knowledge this is the second report where HLH was suspected to be a secondary to CLL and hence given treatment for underlying CLL. There are no randomized trials to base treatment decisions on and the goal of treatment is to suppress inappropriate and uncontrolled inflammatory response. Physicians should have a high index of suspicion for HLH in any patient

who presents with unexplained febrile illness, cytopenias, hepatitis, and encephalitis or multi organ failure. Once the diagnosis is made treatment should be initiated immediately. Further studies are needed to improve outcomes.

References

1. Henter JI, Horne A, Arico M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatric Blood and Cancer* 2007;**48**(2)124–31.
2. Fisman DN. Hemophagocytic syndromes and infection. *Emerging Infectious Diseases* 2000;**6**(6)601–8.
3. Blom A, Beylot-Barry M, D'Incan M, Laroche L. Lymphoma-associated hemophagocytic syndrome (LAHS) in advanced-stage mycosis fungoides/Sezary syndrome cutaneous T-cell lymphoma. *Journal of the American Academy of Dermatology* 2011;**65**(2)404–10.
4. Turner JH, Loyo M, Lin SY. Aggressive sinonasal natural killer/T-cell lymphoma with hemophagocytic lymphohistiocytosis. *American Journal of Otolaryngology* 2012;**33**(1)188–91.
5. Yeh YM, Chang KC, Chen YP, et al. Large B cell lymphoma presenting initially in bone marrow, liver and spleen: an aggressive entity associated frequently with haemophagocytic syndrome. *Histopathology* 2010;**57**(6)785–95.
6. Wang LX, Fei XM, Lu YL, et al. Acute myeloid leukemia initially presenting as hemophagocytic lymphohistiocytosis—a case report and review of the literature. *Leukemia Research* 2010;**34**(1)e46–49.
7. Manoharan A, Catovsky D, Lampert IA, Al M, Gordon-Smith EC, Galton DA. Histiocytic medullary reticulosis complicating chronic lymphocytic leukaemia: malignant or reactive? *Scandinavian Journal of Haematology* 1981;**26**(1)5–13.
8. Chaker L, Segeren CM, Bot FJ, Maartense E. Haemophagocytic syndrome and Hodgkin's disease variant of Richter's syndrome after fludarabine for CLL. *European Journal of haematology* 2010;**85**(1)91–2.
9. Rao RD, Morice WG, Phyliky RL. Hemophagocytosis in a patient with chronic lymphocytic leukemia and histoplasmosis. *Mayo Clinic Proceedings. Mayo Clinic* 2002;**77**(3)287–90.
10. Meki A, O'Connor D, Roberts C, Murray J. Hemophagocytic lymphohistiocytosis in chronic lymphocytic leukemia. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 2011;**29**(24)e685–687.